WHAT IS CLAIMED IS:

1. An antibody that binds specifically to an autophosphorylated form of Inositol Requiring 1 (IRE1).

2. The antibody of claim 1, wherein the antibody is a monoclonal antibody.

3. The antibody of claim 1, wherein the antibody is an antigen-binding fragment of a monoclonal antibody.

4. The antibody of claim 3 wherein the fragment comprises an Fab, $F(ab')_2$, Fv or single chain Fv.

5. The antibody of claim 1, wherein the antibody is a polyclonal antibody.

6. The antibody of claim 5, wherein the polyclonal antibody is PIRE1A1.

7. A method of determining an endoplasmic reticulum (ER) stress level in a cell or biological sample, the method comprising detecting an Inositol Requiring 1 (IRE1) activity level in the cell or biological sample, wherein an increase in the IRE1 activity level indicates an increase in ER stress, and a decrease in the IRE1 activity level indicates a decrease in ER stress.

8. The method of claim 7, wherein the IRE1 activity level is detected by detecting an X-Box-Binding Protein-1 (XBP-1) splicing level.

9. The method of claim 8, wherein the XBP-1 splicing level is determined by:

amplifying an XBP-1 mRNA region that includes a splice site, or portion thereof; and

detecting the size of the amplified mRNA region, wherein the size is indicative of spliced or unspliced mRNA.

10. The method of claim 9, wherein the amplified mRNA is digested with a restriction enzyme.

11. The method of claim 10, wherein the restriction enzyme is Pst I.

12. The method of claim 7, wherein the IRE1 activity level is detected by detecting the level of autophosphorylated IRE1.

13. The method of claim 7, wherein an IRE1 activity level is detected by detecting the ratio of autophosphorylated to unphosphorylated IRE1.

14. The method of claim 13, wherein the level of phosphorylated IREl is detected using an antibody that binds specifically to an autophosphorylated form of IRE1.

15. The method of any one of claims 7-14, wherein the ER stress level is determined in a cell.

16. The method of any one of claims 7-14, wherein the ER stress level is determined in a mammalian cell.

17. The method of any one of claims 7-14, wherein the ER stress level is determined in a human cell.

18. The method of any one of claims 15-17, wherein the cell is a pancreatic beta cell or a peripheral lymphocyte.

19. The method of any one of claims 7-18, wherein the ER stress level is determined in a cell extract.

20. A method of diagnosing an ER stress disorder in a subject, the method comprising determining a level of ER stress in a sample comprising a cell isolated from the subject, using a method according to any one of the preceding claims 7-19, wherein an increased level of ER stress is indicative of an ER stress disorder in the subject.

21. A method of monitoring the progression of an ER stress disorder in a subject, the method comprising determining a level of ER stress in two or more samples comprising a peripheral blood cell isolated from the subject at sequential time points, using a method according to any one of claims 7-19, wherein a change in level of ER stress indicates the progress of the ER stress disorder.

22. The method of claim 20 or 21, wherein the ER stress disorder is diabetes.

23. The method of any one of claims 20-22, wherein the cell is a peripheral blood cell.

24. A method of identifying a test compound that modulates endoplasmic reticulum (ER) stress, the method comprising:

providing an ER stress model system;

optionally, increasing ER stress in the system;

contacting the system with a test compound; and

evaluating one or more of:

(i) a level of Inositol Requiring 1 (IRE1)activity in the system in the presence and absence of the test compound, and/or

(ii) a level of HMG-CoA Reductase Degradation (HRD1) activity in the system in the presence and absence of the test compound,

wherein an increase in the level of IRE1 activity, and/or an increase in the level of HRD1 activity indicates that the test compound causes an increase in ER stress, and a decrease in the level of IRE1 activity indicates that the test compound causes a decrease in ER stress.

25. The method of claim 24, wherein the ER stress model system is a cell or animal model of an ER stress disorder.

26. The method of claim 24, wherein ER stress in the system is increased by contacting the system with an agent that increases levels of ER stress.

27. The method of claim 26, wherein the agent that increases ER stress is thapsigargin or tunicamycin.

28. The method of claim 24, wherein the level of IRE1 activity is evaluated by measuring levels of XBP-1 splicing.

29. The method of claim 24, wherein the level of IRE1 activity is evaluated by measuring levels of IRE1 autophosphorylation.

30. The method of claim 29, wherein the level of IRE1 autophosphorylation is measured using an antibody that binds specifically to the autophosphorylated form of IRE1.

31. A kit for determining ER stress, the kit comprising:

one or more primers for amplifying a region of X-Box-Binding Protein-1 (XBP-1) mRNA that includes a splice site, or portion thereof;

one or more of: a control comprising a spliced XBP-1 nucleic acid and a control comprising an unspliced XBP-1 nucleic acid; and

instructions for use.

32. The method of claim 24, further comprising:

contacting an ER stress model system with a candidate compound that increases IRE1 and/or HRD1 activity; and

evaluating ER stress in the system in the presence of the candidate compound,

wherein a decrease in ER stress in the system in the presence of the candidate compound indicates that the candidate compound is a candidate therapeutic agent for the treatment of an ER stress disorder.

33. The method of claim 24, further comprising:

providing a model of an ER stress disorder;

optionally, increasing levels of ER stress in the model;

contacting the model with a candidate therapeutic agent for the treatment of an ER stress disorder identified by the method of claim 33; and

evaluating the levels of ER stress in the system in the presence of the candidate compound,

wherein an improvement in the model in the presence of the candidate therapeutic agent indicates that the agent is a therapeutic agent for the treatment of an ER stress disorder.

34. The method of any of claims 24-33, wherein the compound or agent is a nucleic acid, polypeptide, peptide, or small molecule.

35. The method of claim 34, wherein the compound or agent is an HRD1 nucleic acid, polypeptide, or a functional fragment thereof.

36. The method of claim 35, wherein the functional fragment is or encodes a peptide comprising a cytosolic RING-H2 domain of HRD1 or a homolog thereof.

37. The method of claim 35, wherein the functional fragment is or encodes a peptide comprising amino acids 291-333 of SEQ ID NOs:40 or 42.

38. The method of claim 35, wherein the functional fragment is or encodes a peptide comprising amino acids 272-243 of SEQ ID NOs:40 or 42.

39. A therapeutic composition for the treatment of an ER stress disorder comprising an HRD1 nucleic acid, polypeptide, or a functional fragment thereof and a pharmaceutically acceptable carrier.

40. The therapeutic composition of claim 39, wherein the functional fragment is or encodes a peptide comprising a cytosolic RING-H2 domain of HRD1 or a homolog thereof.

41. The therapeutic composition of claim 39, wherein the functional fragment is or encodes a peptide comprising amino acids 291-333 of SEQ ID NOs:40 or 42.

42. The therapeutic composition of claim 39, wherein the functional fragment is or encodes a peptide comprising amino acids 272-243 of SEQ ID NOs:40 or 42.

43. A method of treating a subject having or at risk of developing an ER stress disorder, the method comprising administering to the subject a therapeutically effective amount of a therapeutic agent identified by the method of claim 33.

44. A method of treating a subject having or at risk of developing an Endoplasmic Reticulum (ER) stress disorder, the method comprising administering to the subject a therapeutically effective amount of an HMG-CoA Reductase Degradation (HRD1) nucleic acid, polypeptide, or functional fragment thereof.

45. An HMG-CoA Reductase Degradation (HRD1) nucleic acid, polypeptide, or functional fragment thereof for use in the treatment of an ER stress disorder.

46. The use of an HMG-CoA Reductase Degradation (HRD1) nucleic acid, polypeptide, or functional fragment thereof in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of an ER stress disorder.